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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,060	07/10/2000	Neil Andrew Williams	CTH-03	6761

7590 07/16/2002

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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	16

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/600,060	Applicant(s) WILLIAMS ET AL.
	Examiner " Neon" Phuong Huynh	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 49-65 are pending.

2. Claims 49-65 are being acted upon in this Office Action.

3. Claim 51 is objected to because of misspelling "signalling".

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 49-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of screening agent such as EtxB (G33D), EtxB that binds to GM1 wherein said EtxB (G33D) is capable of modulating ganglioside associated activity by measuring the levels of cytokines such as IL-2, IL-4, IL-5, IL-10 and IFN-γ and antigen specific IgA in vitro, **does not** reasonably provide enablement for (1) a method of **treating** a subject for *any* allergic or hypersensitivity condition such as asthma comprising administering to the subject an effective amount of (2) *any* agent that is capable of modulating a ganglioside-associated activity, (3) *any* agent capable of blocking an IgE mediated response, (4) *any* agent exhibits GM1 binding activity, or has an effect on GM1 mediated intracellular signaling events but no GM1 binding activity, (5) *any* agent is *any* mutants or derivatives of Etx, Ctx, CtxB, or EtxB, wherein said agent is not coupled to *any* antigen, (6) a method for treating a subject for an allergic or hypersensitivity condition comprising administering to the subject an effective amount of *any* agent that modifies a GM1 associated activity, *any* agent that binds to GM1, *any* agent that reduces levels of serum antigen specific IgE, wherein said agent is not coupled to *any* antigen, (9) a method for treating a subject for *any* allergic or hypersensitivity condition comprising administering to the subject an effective amount of *any* agent such as mutant or derivative of CtxB, EtxB that modifies a GM1-associated activity and is not coupled to *any* antigen for treatment of asthma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only five agents such as Etx, Ctx, EtxB, CtxB, and EtxB (G33D), which is a mutant or derivative of EtxB, and a method of screening agent such as EtxB (G33D), EtxB that binds to GM1 wherein the EtxB (G33D) mutant is capable of modulating ganglioside associated activity by measuring the levels of cytokines such as IL-2, IL-4, IL-5, IL-10 and IFN-γ and antigen specific IgA in vitro. The specification defines the term "ganglioside associated activity" includes *any* one or more of modulating or immunomodulating a ganglioside receptor, modulating any signaling event prior to, during or subsequent to ganglioside receptor binding (page 15, lines 7-9). Further, the specification defines "agent capable of modulating a ganglioside associated activity" can be used to describe *any* agent, which acts as an immunomodulator through interacting with a ganglioside (See page 17, lines 1-3). The specification defines the term "allergic condition" includes but not limited to asthma and the term "hypersensitivity condition" includes but is not limited to conditions such as contact hypersensitivity such as plant poison ivy (page 20).

The specification does not teach a method of **treating** a subject for *any* allergic or hypersensitivity condition such as asthma comprising administering to the subject an effective amount of *any* agent mentioned above. There is insufficient guidance and working example as how to make *any* agent, *any* mutants or derivatives of Etx, Ctx, CtxB, or EtxB that is capable of modulating *any* ganglioside associated activity since an agent could be any agent which acts as an immunomodulator through interacting with a ganglioside and modulating any signaling event prior to, during or subsequent to ganglioside receptor binding (page 15, lines 7-9). There is no structure associated with the term "agent" since an agent can be DNA, RNA, protein, and small organic molecule. Further, the term "modulating" can be inhibitory as well as stimulatory, which are mutually exclusive.

Aman *et al* teach a mutant of cholera toxin B subunit (CtxB) such as CtxB (H57A) that has a single amino acid substitution from His to Ala lost its immunomodulatory activity although it still binds GM1 ganglioside (See entire document, abstract, in particular). Given the indefinite number of agent, and mutants or derivatives of Etx, Ctx, CtxB, or EtxB, it is unpredictable which undisclosed agent would be useful for treating *any* allergic or hypersensitivity condition such as asthma. Further, there is no in vivo data of using *any* agent, *any* mutants or derivatives of Etx, Ctx, CtxB, or EtxB mentioned above, including the only EtxB (G33D) mutant that fails to bind to GM1 but is capable of modulating ganglioside associated activity for treating *any* allergic or hypersensitivity condition such as asthma. A method of treatment in the absence of in vivo data are unpredictable for the following reasons: (1) the agent, mutant or derivative thereof may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the agent; (2) the agent may not reach the target area because, i.e. the agent may not be able to cross the mucosa or the agent may be adsorbed by fluids, cells and tissues where the agent has no effect; and (3) other functional properties, known or unknown, may make the agent unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Therefore, it would require undue experimentation of even one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

6. Claims 49-65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method of **treating** a subject for *any* allergic or hypersensitivity condition such as asthma comprising administering to the subject an effective amount of *any* agent that is capable of modulating a ganglioside-associated activity, *any* agent capable of blocking an IgE mediated response, *any* agent exhibits GM1 binding activity, or has an effect on GM1 mediated intracellular signaling events but no GM1 binding activity, *any* agent is *any* mutants or derivatives of Etx, Ctx, CtxB, or EtxB, wherein said agent is not coupled to *any* antigen, (2) a method for treating a subject for an allergic or hypersensitivity condition comprising administering to the subject an effective amount of *any* agent that modifies a GM1 associated activity, *any* agent that binds to GM1, *any* agent that reduces levels of serum antigen specific IgE, wherein said agent is not coupled to *any* antigen, (3) a method for treating a subject for *any* allergic or hypersensitivity condition comprising administering to the subject an effective amount of *any* agent such as mutant or derivative of CtxB, EtxB that modifies a GM1-associated activity and is not coupled to *any* antigen for treatment of asthma.

The specification discloses only five agents such as Etx, Ctx, EtxB, CtxB, and EtxB (G33D), which is a mutant or derivative of EtxB, and a method of screening agent such as EtxB (G33D), EtxB that binds to GM1 wherein the EtxB (G33D) mutant is capable of modulating ganglioside associated activity by measuring the levels of cytokines such as IL-2, IL-4, IL-5, IL-10 and IFN-γ and antigen specific IgA in vitro. The specification defines the term "ganglioside associated activity" includes *any* one or more of modulating or immunomodulating a ganglioside receptor, modulating any signaling event prior to, during or subsequent to ganglioside receptor binding (page 15, lines 7-9). Further, the specification defines "agent capable of modulating a ganglioside associated activity" can be used to describe *any* agent, which acts as an immunomodulator through interacting with a ganglioside (See page 17, lines 1-3). The specification defines the term "allergic condition" includes but not limited to asthma and the term "hypersensitivity condition" includes but is not limited to conditions such as contact hypersensitivity such as plant poison ivy (page 20).

With the exception of the specific Etx, Ctx, EtxB, CtxB, and EtxB (G33D) mentioned above, there is insufficient written description about the structure associated with function of (1) *any* agent and (2) *any* mutants or derivatives of Etx, Ctx, CtxB, or EtxB. Further, the specification discloses only one mutant EtxB (G33D) that is a derivative of EtxB. Given the lack of a written description of *any* additional representative species of mutant or derivative, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 49-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "modulating" in claim 49 is indefinite and ambiguous because the term "modulating" could be stimulatory **or** inhibitory. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 49, 51-53, 55, 56-57, 59, and 61-63 are rejected under 35 U.S.C. 103(a) as being unpatentable WO 95/10301 publication (April 1995, PTO 1449) in view of WO 97/02045 publication (Jan 1997, PTO 1449) or Nashar *et al* (Proc Natl Acad Sci 93: 226-30, Jan 1996; PTO 1449).

The WO 95/10301 publication teaches a method for treating a subject for hypersensitivity condition such as allergy or delayed-type-hypersensitivity (DTH) reactions to human gamma globulins comprising administering to the subject such as mice an effective amount of an agent such as B subunit of *E coli* heat-labile enterotoxin (LTB) or the B subunit of cholera toxin (CTB) conjugated to an antigen such as human gamma globulins or Red blood cell (RBC) (See pages 23, 24, Example 1, pages 26 and 32, Tables 2-9, claims 16, 1-5, 8, 9, in particular). The reference LTB and CTB bind to GM1 (See page 17, lines 23-30, in particular) and have an effect on GM1 mediated intracellular signaling events such as prolonged graft survival, suppression of EAE (See pages 28-29, in particular). The reference LTB and CTB are the same as the claimed EtxB and CtxB, respectively.

The claimed invention as recited in claim 49 differs from the references only by the recitation that the agent is not coupled to an antigen.

The claimed invention as recited in claim 51 differs from the references only by the recitation that the agent has an effect on GM1 mediated intracellular signaling events but no GM1 binding activity.

The claimed invention as recited in claim 52 differs from the references only by the recitation that the agent is selected from the group consisting of Etx, Ctx, CtxB, EtxB and mutants or derivatives thereof that bind to GM1.

The claimed invention as recited in claim 56 differs from the references only by the recitation that the agent modifies a GM1-assciated activity wherein the agent is not coupled to an antigen.

The claimed invention as recited in claim 61 differs from the references only by the recitation that the agent is selected from the group consisting of CtxB, EtxB or a mutant or derivatives thereof that modifies a GM1-associated activity and is not coupled to an antigen.

The WO 97/02045 publication teaches a method for treating a subject comprising administering to the subject such as mice an effective amount of an agent such as B subunit of *E coli* heat-labile enterotoxin (EtxB) or a derivative of EtxB such as EtxB (G33D) which is also a mutant of EtxB having Gly-33 to Asp substitution, and an antigen such as OVA, which is also an allergen, in a mixture (not coupled) (See page 16, in particular). The reference method is useful for induction of tolerance to foreign antigenic determinant (See claim 16 of WO 97/02045, in particular).

Nashar *et al* teach agent such as E. Coli heat-labile enterotoxin (Etx) and closely related homologue cholera toxin (Ctx) EtxB and EtxB (G33D) and their respective B subunits are potent mucosal and systemic immunogens and potential carriers (See page 226, column 1, in particular). The B subunits Etx B and Ctx bind to GM1 and modulate immune response such as serum antibody response (See page 228, Fig 2, in particular). Nashar *et al* further teach agent such as EtxB (G33D), which is a mutant having a Gly to Asp substitution at residue 33 fails to bind to GM1 but has an effect on GM1 mediated intracellular signaling events such as lymphocyte proliferation (Table 1, in particular). Nashar *et al* teach ExtB stimulates B and T cells activation (See Fig 4, in particular) while EtxB (G33D) mutant decreases B and T cell activation, and increases IFNγ production (See Table 2, in particular). Further, the reference teaches EtxB but not EtxB (G33D) causes complete depletion of CD8+ cells by apoptosis (See page 230, column 1, second full paragraph, in particular). Nashar *et al* teach the reference agents' potent immunogenicity is dependent not only on efficient receptor-mediated uptake but also on direct receptor-mediated immunomodulation of lymphocyte subsets (See Abstract, in particular).

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to substitute the agent such as LTB (EtxB) or CTB (CtxB) as taught by the WO 95/10301 publication for the agent such as EtxB (G33D) or EtxB as taught by the WO 97/02045 publication or the Ctx and EtxB (G33D) as taught by Nashar *et al* for a method for treating a subject for allergic or hypersensitivity condition as taught by the WO 95/10301 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the WO 97/02045 publication teaches the reference agent is useful for induction of tolerance to foreign antigenic determinant (See claim 16 of WO 97/02045, in particular). Nashar *et al* teach the reference agents' potent immunogenicity is dependent not only

on efficient receptor-mediated uptake but also on direct receptor-mediated immunomodulation of lymphocyte subsets (See Abstract, in particular).

12. Claims 50, 54, 58, 60, 64 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable WO 95/10301 publication (April 1995, PTO 1449) in view of WO 97/02045 publication (Jan 1997, PTO 1449) or Nashar *et al* (Proc Natl Acad Sci 93: 226-30, Jan 1996; PTO 1449) as applied to claims 49, 51-53, 55, 56-57, 59, and 61-63 mentioned above and further in view of Roitt *et al* (in Immunology, 2nd edition, pages 19.1-19.3, 1989, PTO 892) and Patterson *et al* (J immunol 117(1): 97-101, July 1976, PTO 892).

The teachings of the WO 95/10301 publication, the WO 97/02045 publication and Nashar *et al* have been discussed supra.

The claimed invention as recited in claims 54, 60, and 64-65 differs from the references only by the recitation that the treatment is for asthma.

The claimed invention as recited in claim 50 differs from the references only by the recitation that the agent is capable of blocking an IgE mediated response.

The claimed invention as recited in claim 58 differs from the references only by the recitation that the agent reduces levels of serum antigen-specific IgE.

Roitt *et al* teach hypersensitivity (type I) occurs when an IgE response is directed against innocuous antigen such as pollen, the resulting release of pharmacological mediators such as histamine by IgE sensitized mast cells produces an acute inflammatory reaction with symptoms such as asthma and the levels of IgE are often raised in allergic disease (See page 19.1, page 19.3, column 2, in particular).

Patterson *et al* teach cholera toxin (Ctx) inhibits IgE production (See abstract, in particular).

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to include asthma as one of the hypersensitivity condition as taught by Roitt *et al* using the agent such as LTB (EtxB) or CTB (CtxB) as taught by the WO 95/10301 publication or the agent such as EtxB (G33D) or EtxB as taught by the WO 97/02045 publication or the agent such as Ctx and EtxB (G33D) as taught by Nashar *et al* for a method for treating a subject for allergic or hypersensitivity condition as taught by the WO 95/10301 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Roitt *et al* teach the levels of IgE are often raised in allergic disease (See page 19.1, page 19.3, column 2, in particular) and Patterson *et al* teach cholera toxin (Ctx) inhibits IgE production (See abstract, in particular).

13. Claims 49, 50-53, 55, 56-59, and 61-63 are rejected under 35 U.S.C. 103(a) as being unpatentable Tamura *et al* (Vaccine 15(2): 225-229, 1997, PTO 892) in view of WO 97/02045 publication (Jan 1997, PTO 1449) or Nashar *et al* (Proc Natl Acad Sci 93: 226-30, Jan 1996; PTO 1449).

Tamura *et al* teach a method for treating a subject for hypersensitivity condition such as allergy or delayed-type-hypersensitivity (DTH) reactions comprising administering to the subject such as mice an effective amount of an agent such as B subunit of *E coli* heat-labile enterotoxin (LTB) or LT coupled or conjugated to an antigen such as ovalbumin (See abstract, page 227, column 1, in particular). The reference LTB and CTB bind to GM1 (See page 226, Preparation of LTB-LT conjugated antigen, in particular). The reference LT and LTB are the same as the claimed Etx and EtxB, respectively. The reference ovalbumin (OVA) coupled to LTB suppresses the induction of both DTH and IgE antibody responses (See page 225, column 2,Table 1, in particular). Tamura *et al* teach LTB-coupled OVA is useful for suppressing the induction of both DHT and IgE antibody responses and LTB as well as CTB can serve as a powerful carrier induction of immunologial tolerance (See page 228, column 1, first full paragraph, in particular).

The claimed invention as recited in claim 49 differs from the references only by the recitation that the agent is not coupled to an antigen.

The claimed invention as recited in claim 51 differs from the references only by the recitation that the agent has an effect on GM1 mediated intracellular signaling events but no GM1 binding activity.

The claimed invention as recited in claim 52 differs from the references only by the recitation that the agent is selected from the group consisting of Etx, Ctx, CtxB, EtxB and mutants or derivatives thereof that bind to GM1.

The claimed invention as recited in claim 56 differs from the references only by the recitation that the agent modifies a GM1-assciated activity wherein the agent is not coupled to an antigen.

The claimed invention as recited in claim 61 differs from the references only by the recitation that the agent is selected from the group consisting of CtxB, EtxB or a mutant or derivatives thereof that modifies a GM1-associated activity and is not coupled to an antigen.

The WO 97/02045 publication teaches a method for treating a subject comprising administering to the subject such as mice an effective amount of an agent such as B subunit of *E coli* heat-labile enterotoxin (EtxB) or a derivative of EtxB such as EtxB (G33D) which is also a mutant of EtxB having Gly-33 to Asp substitution, and an antigen such as OVA, which is also an allergen, in a mixture (See page 16, in particular). The reference method is useful for induction of tolerance to foreign antigenic determinant (See claim 16 of WO 97/02045, in particular).

Nashar *et al* teach agent such as E. Coli heat-labile enterotoxin (Etx) and closely related homologue cholera toxin (Ctx) EtxB and EtxB (G33D) and their respective B subunits are potent mucosal and systemic immunogens and potential carriers (See page 226, column 1, in particular). The B subunits of Etx B and Ctx bind to GM1 and modulate immune response such as serum antibody response (See page 228, Fig 2, in particular). Nashar *et al* further teach agent such as EtxB (G33D), which is a mutant having a Gly to Asp substitution at residue 33 fails to bind to GM1 but has an effect on GM1 mediated intracellular signaling events such as lymphocyte proliferation (Table 1, in particular). Nashar *et al* teach ExtB stimulates B and T cells activation (See Fig 4, in particular) while EtxB (G33D) mutant decreases B and T cell activation, and increases IFNγ production (See Table 2, in particular). Further, the reference teaches EtxB but not EtxB (G33D) causes complete depletion of CD8+ cells by apoptosis (See page 230, column 1, second full paragraph, in particular). Nashar *et al* teach the reference agents' potent immunogenicity is dependent not only on efficient receptor-mediated uptake but also on direct receptor-mediated immunomodulation of lymphocyte subsets (See Abstract, in particular).

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to use unconjugated agent such as EtxB (G33D) or EtxB as taught by the WO 97/02045 publication or the unconjugated Ctx and EtxB (G33D) as taught by Nashar *et al* for a method for treating a subject for allergic or hypersensitivity condition as taught by the Tamura *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Tamura *et al* teach LTB as well as CTB can serve as a powerful carrier induction of immunologial tolerance such as DHT and IgE responses (See page 228,

column 1, first full paragraph, in particular). The WO 97/02045 publication teaches the reference agent is useful for induction of tolerance to foreign antigenic determinant (See claim 16 of WO 97/02045, in particular). Nashar *et al* teach the reference agents' potent immunogenicity is dependent not only on efficient receptor-mediated uptake but also on direct receptor-mediated immunomodulation of lymphocyte subsets (See Abstract, in particular).

14. Claims 54, 60, and 64-65 are rejected under 35 U.S.C. 103(a) as being unpatentable Tamura *et al* (Vaccine 15(2): 225-229, 1997, PTO 892) in view of WO 97/02045 publication (Jan 1997, PTO 1449) or Nashar *et al* (Proc Natl Acad Sci 93: 226-30, Jan 1996; PTO 1449) as applied to claims 49, 50-53, 55, 56-59, and 61-63 mentioned above, and further in view of Roitt *et al* (in Immunology, 2nd edition, pages 19.1-19.3, 1989, PTO 892).

The teachings of Tamura *et al*, the WO 97/02045 publication and Nashar *et al* have been discussed supra.

The claimed invention as recited in claims 54, 60, and 64-65 differs from the references only by the recitation that the treatment is for asthma.

Roitt *et al* teach hypersensitivity (type I) occurs when an IgE response is directed against innocuous antigen such as pollen, the resulting release of pharmacological mediators such as histamine by IgE sensitized mast cells produces an acute inflammatory reaction with symptoms such as asthma and the levels of IgE are often raised in allergic disease (See page 19.1, page 19.3, column 2, in particular).

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to include asthma as one of the hypersensitivity condition as taught by Roitt *et al* using the agent such as LTB (EtxB) or LT (Etx) as taught by Tamura *et al* or the agent such as EtxB (G33D) or EtxB as taught by the WO 97/02045 publication or the agent such as Ctx and EtxB (G33D) as taught by Nashar *et al* for a method for treating a subject for allergic or hypersensitivity condition as taught by the WO 95/10301 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Roitt *et al* teach the levels of IgE are often raised in allergic disease (See page 19.1, page 19.3, column 2, in particular) and Patterson *et al* teach cholera toxin (Ctx) inhibits IgE production (See abstract, in particular). Tamura *et al* teach LTB as well as CTB can

serve as a powerful carrier induction of immunologial tolerance such as DHT and IgE responses (See page 228, column 1, first full paragraph, in particular).

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

17. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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